

THE SIMONS CENTER FOR THE SOCIAL BRAIN (SCSB) NEWSLETTER | Spring 2019

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PUBLICATION SPOTLIGHT

- Allison Fitch, Annalisa Valadez, Patricia A. Ganea, Alice S. Carter, and **Zsuzsa Kaldy**. [Toddlers with Autism Spectrum Disorder can use language to update their expectations about the world](#). *Journal of Autism and Developmental Disorders* 49 (2):429-440 [<https://doi.org/10.1007/s10803-018-3706-7>], August 2018. (or February 2019 – when appeared in Journal)

- Ken-ichi Amemori, Satoko Amemori, Daniel J. Gibson, and **Ann M. Graybiel**. [Striatal Microstimulation Induces Persistent and Repetitive Negative Decision-Making Predicted by Striatal Beta-Band Oscillation](#). *Neuron* 99:829–841 [<https://doi.org/10.1016/j.neuron.2018.07.022>], August 2018.

- **Alexandra Krol**, Ralf D. Wimmer, **Michael M. Halassa**, and **Guoping Feng**. [Thalamic Reticular Dysfunction as a Circuit Endophenotype in Neurodevelopmental Disorders](#). *Neuron* 98:282-295 [<https://doi.org/10.1016/j.neuron.2018.03.021>], April 2018.

- Cristina Mei, **Evelina Fedorenko**, David J. Amor, Amber Boys, Caitlyn Hoefflin, Peter Carew, Trent Burgess, Simon E. Fisher, and **Angela T. Morgan**. [Deep phenotyping of speech and language skills in individuals with 16p11.2 deletion](#). *European Journal of Human Genetics* 26(5):676-686 [<https://doi.org/10.1038/s41431-018-0102-x>], February 2018.

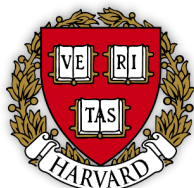
- Ali Barandov, Benjamin B. Bartelle, Catherine G. Williamson, Emily S. Loucks, Stephen J. Lippard, and **Alan Jasanoff**. [Sensing intracellular calcium ions using a manganese-based MRI contrast agent](#). *Nature communications* 10(1):897 [<https://doi.org/10.1038/s41467-019-08558-7>], February 2019.

SCSB COLLABORATIONS

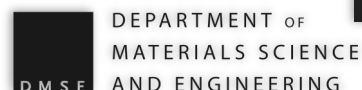
EXTERNAL COLLABORATIONS



Northeastern University
Bouvé College of Health Sciences



INTERNAL MIT COLLABORATIONS



TARGETED PROJECT UPDATES:

THE MARMOSET TARGETED PROJECT: BUILDING COLLABORATIONS

The targeted project on ‘Circuit mechanisms of ASD-relevant behaviors in marmosets’ aims to develop marmosets as a model system to study complex behaviors and understand their neural circuit substrates. As a first step, the project will focus on behaviors and circuits relevant to autism spectrum disorders in wild-type marmosets. Success of the project would enable analysis, in the future, of genetic models of ASD utilizing CRISPR genome-editing technology to directly manipulate the marmoset genome. The four components of the project reveal a great deal of collaborative work in progress.

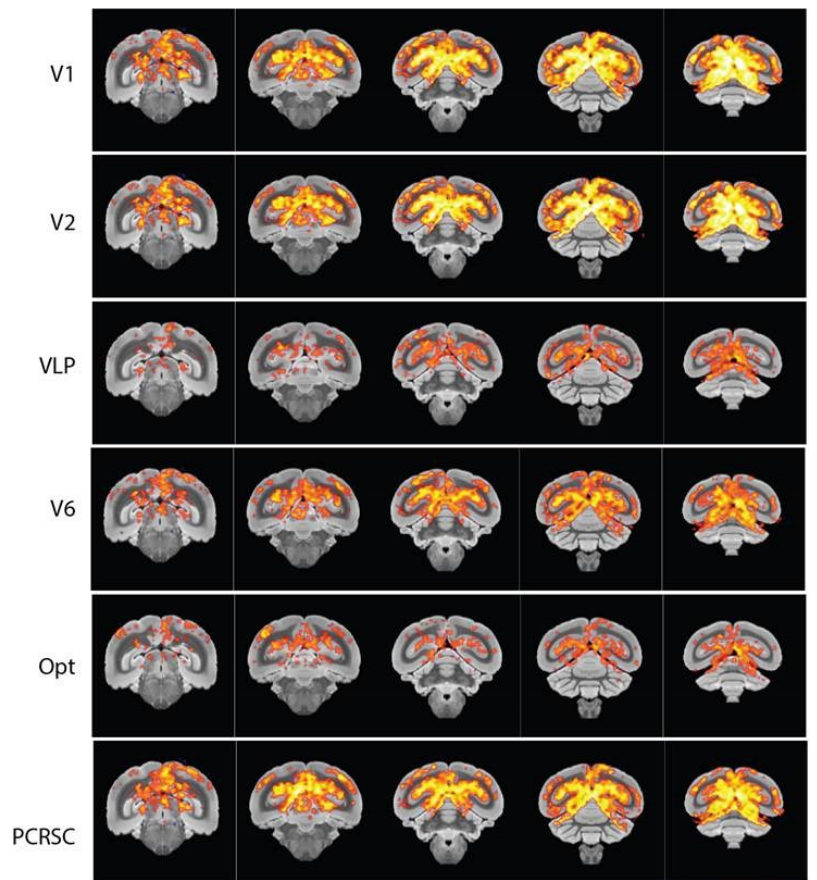
Robert Desimone’s lab is studying the neural circuitry of social attention and cognition in wild type marmosets. To map the social brain, the lab is focusing on fMRI and electrophysiological recordings using ECoG arrays. They have trained marmosets to adapt to a specially designed MRI cradle with custom designed multichannel MR coils and head and body restraint. To extract functional neural signals associated with visual social information, marmosets are being scanned in a Bruker Biospin 9.4 tesla scanner in collaboration with the Jasanoff and Sur labs.

Work in Ann Graybiel’s lab investigates a hallmark feature of ASD, repetitive or perseverative behaviors, and involvement of the striatum in such behaviors. Their initial focus is on establishing markers of striosomal and matrix compartments as well as markers of connectivity and gene regulation. In collaboration with the Desimone and Feng labs, they are developing behavioral scores in order to evaluate correlations between striosomal activation and spontaneous stereotypic behavior.

Disruption in excitation (E) – inhibition (I) balance has been proposed as a circuit level mechanism of

ASD. Mriganka Sur’s lab is testing this hypothesis in the context of temporal processing and prediction. They have developed a home-cage training system and task in which marmosets are required to predict when an image appears or disappears. Pharmacological and optogenetic manipulation of intracortical inhibition, in collaboration with the Feng lab, will be used to test the role of E-I balance in temporal expectation, reaction times, and neuronal response correlates.

The Jasanoff lab’s goal is to study brain functions in marmosets by advanced whole-brain imaging techniques such as ultrahigh resolution MRI. In collaboration with Desimone and Sur labs, they are developing imaging protocols for structural and functional MRI in anesthetized and awake marmosets. They have successfully collected high-resolution anatomical images and resting state BOLD fMRI images in awake marmosets. In addition, they are developing neurotransmitter-sensitive functional MRI methods for whole-brain marmoset imaging.

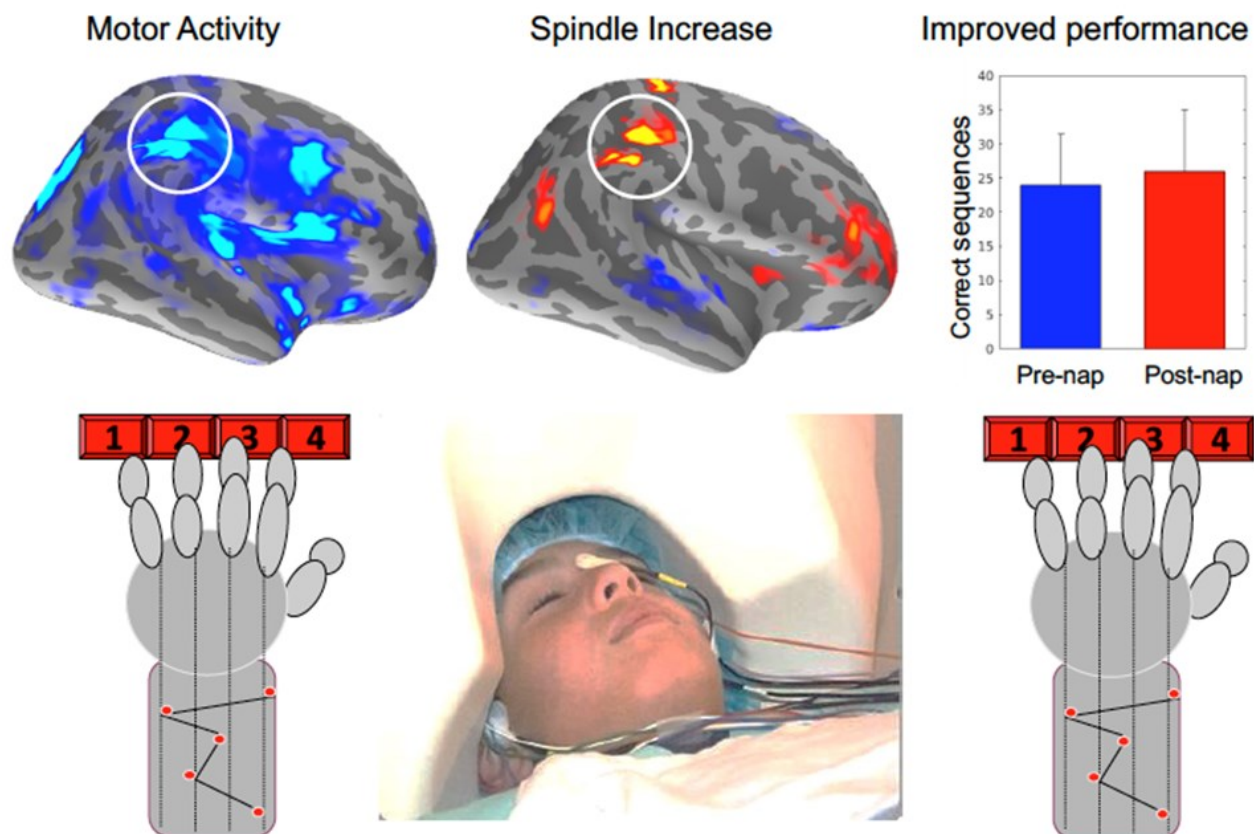


Correlation maps with seeds in V1, V2, VLP, V6, Opt and PCRSC. Data from resting state EPI imaging of 20min on an awake marmoset. Inplane 500*500um, thickness 2mm.

THALAMIC INVOLVEMENT IN ASD, FROM SENSORY AND COGNITIVE PROCESSING TO SLEEP

The targeted project on the 'Role of the Thalamic Reticular Nucleus (TRN) in thalamocortical coordination, cognitive processing and sleep in ASD' combines human and rodent electrophysiological approaches with mouse genetic models and gene-editing technology (CRISPR) to assess whether TRN dysfunction contributes to the manifestations of ASD symptoms. Over the past two years, the team of four laboratories has made important discoveries toward the identification of electrophysiological signatures and molecular targets that may relate to brain mechanisms underlying core ASD symptoms. Their work is an important first step toward the development of scalable biomarkers of TRN function that could be used for screening and tracking the progression of ASD.

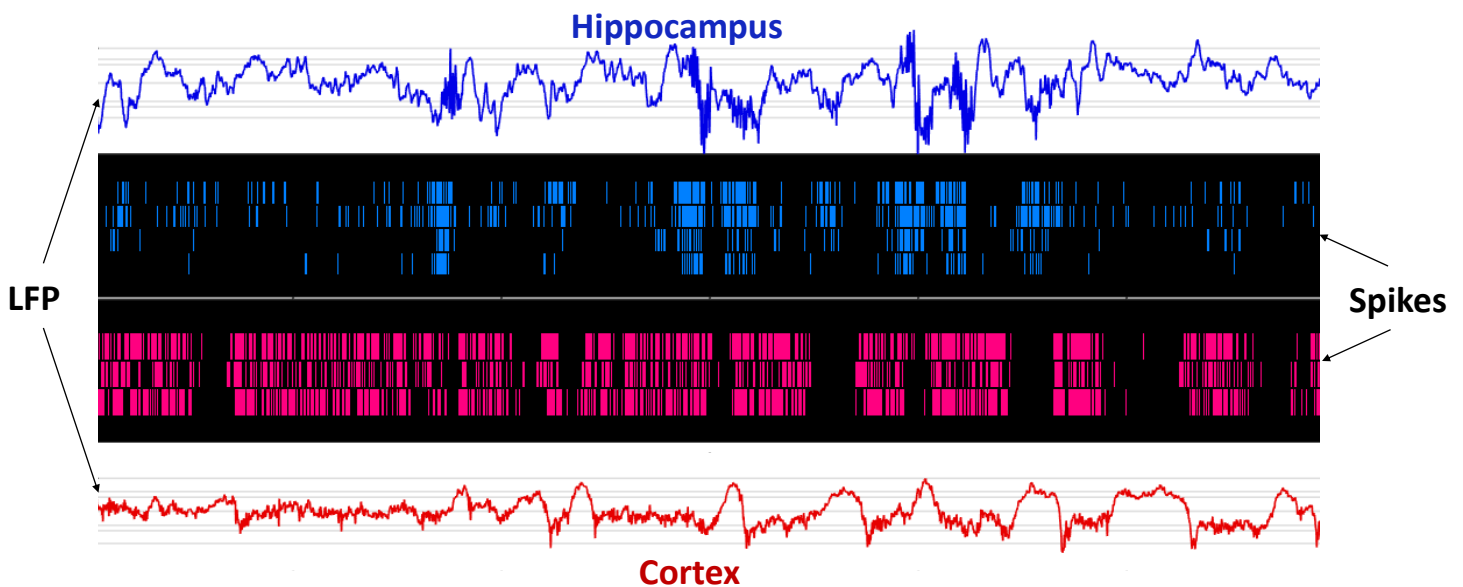
Dara Manoach's lab at Harvard/MGH is using simultaneous magnetoencephalography and EEG to examine sleep spindles – brain rhythms that are generated by the TRN during sleep, and that facilitate memory consolidation. Their findings in neurotypical individuals work show that learning a finger tapping task leads to increased spindle activity in the nap that follows, particularly in the motor regions that were active during learning. Following the nap, performance improves. This suggests that spindles act locally, in brain networks involved in learning, to consolidate memory during sleep. They are now examining whether individuals with ASD show the same focal increases in spindles and the same memory benefits.



Using simultaneous MEG and EEG allows localization of cortical activity that is associated with sleep-dependent enhancement of motor memory in both typically developing individuals and those with autism.

Work in the laboratory of Guoping Feng at MIT demonstrated that the TRN exhibits neuronal heterogeneity in terms of anatomical localization, connectivity and key electrophysiological properties involved in the generation of delta and spindle oscillations during sleep. This work allowed them to modulate sleep oscillations *in vivo* by manipulating separate TRN subnetworks with different gene expression profiles. In an effort to develop tools that target domain-specific TRN sub-regions that may be selectively involved in ASD, they also developed a CRISPR-based assay that knocks out TRN enriched ASD risk genes *in vivo*. This assay will allow the examination of potential perturbations in TRN electrophysiological properties that mediate sleep oscillatory activity and sensory processing and their link to ASD.

Using simultaneous recordings of populations of neurons in the TRN, hippocampus and cortex of freely behaving rodents, work in Matt Wilson's lab at MIT has identified periods of synchronous activity between these brain structures during wake and sleep. These periods of increased coordination are characterized by the reactivation of recent memories in the hippocampus of both rats and mice. Their work in rats showed that involvement of these areas during awake memory replay was necessary for the successful execution of a decision-making task that required the integration of temporally disjoint information. Interestingly, the coordination between TRN, cortex and hippocampus is disrupted in a mouse model of ASD with TRN dysfunction. Their ongoing work is testing whether manipulating TRN optogenetically can restore synchronous activity in the affected brain regions and support the integration of new information in this mouse model of ASD.



Simultaneous recording of neuronal activity in hippocampus (blue) and cortex (red) during sleep in mice.

The Halassa lab at MIT has tested the role of the TRN in goal-directed behavior and has found that goal representations in cortical areas involved in executive control are affected in a mouse model of ASD with TRN deficits. In an effort to identify potential treatment strategies for human patients, they have been able to rescue this behavioral deficit by administering pharmacological agents known to act through the cognitive mediadorsal thalamus (MD). Their current work focuses on identifying whether TRN regulation of the MD thalamus is also affected in mouse models of ASD and examining strategies that target cortical and thalamic networks to restore executive control.

For additional information on Targeted Projects, please visit: <http://scsb.mit.edu/research/>

SIMONS POSTDOCTORAL FELLOWS:

Will Menegas, Ph.D. [Feng lab, McGovern Institute, MIT]

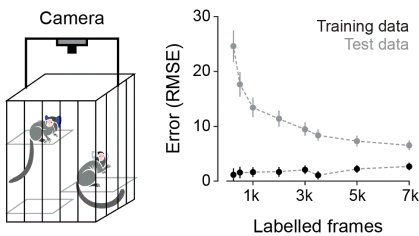
MEASURING SOCIAL BEHAVIOR IN MARMOSETS

The common marmoset is emerging as a model organism for the study of neurological disorders affecting complex behaviors, such as autism spectrum disorders. Establishing quantitative methods for measuring marmoset social behaviors is an important first step toward their use as a model. In recent years, methods for automated image labeling and analysis have been developed for several model organisms such as worms, fruit flies, zebrafish, and mice. We developed and applied similar methods to study marmoset social behavior.

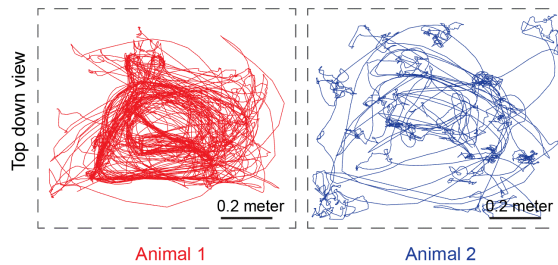
First, we trained a deep network to separately detect multiple marmosets in videos (A), allowing us to track them throughout prolonged videos (B). Next, we developed behavioral metrics to quantitatively describe their social behavior. To manipulate social behavior, we designed a task in which animals can obtain rewards by attending to visual and auditory cues in separate rooms (C). We measured animals' behavior during the delay between trials and found that they were much less social during the task, based on several simple metrics (D).



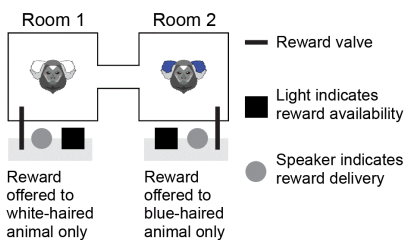
A Training a deep network to label animals



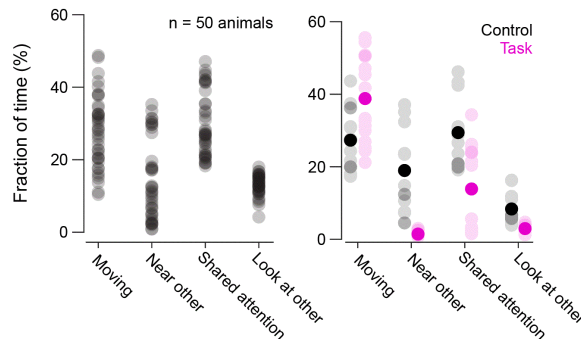
B Example paths



C Offer animals reward in different rooms



D Task-related changes in social behavior



This study will help establish both a computational and experimental basis for studies of marmoset social behavior. In particular, we will use these methods to compare the social behavior of typically developing or ASD model animals in social housing chambers.

Measuring social behavior in marmosets **A)** Left: Schematic of camera placement for video recording. Right: Network was trained until reaching asymptotic accuracy. **B)** Example traces of the head position of animal 1 (red) and animal 2 (blue) during a brief recording session. **C)** Schematic of task design. A light indicates reward availability, and animals can receive reward by approaching the valve in their chamber. After the reward is delivered, there is a timeout before it is available again. **D)** Task-related changes in basic parameters such as time spent moving, time spent near other animal, frequency of looking in the same direction (shared attention) and frequency of looking at the other animal.

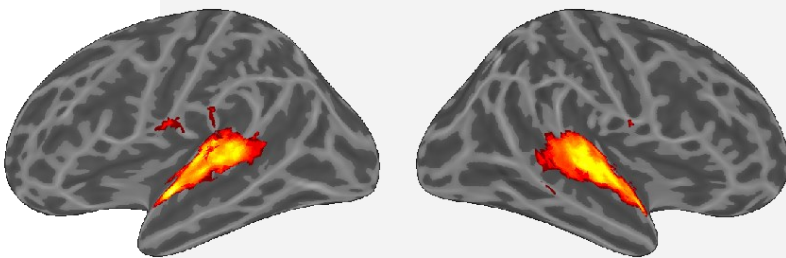
Anila D’Mello, Ph.D. [John Gabrieli Laboratory, MIT]

CHARACTERIZING NEURAL ADAPTATION IN AUTISM SPECTRUM DISORDER



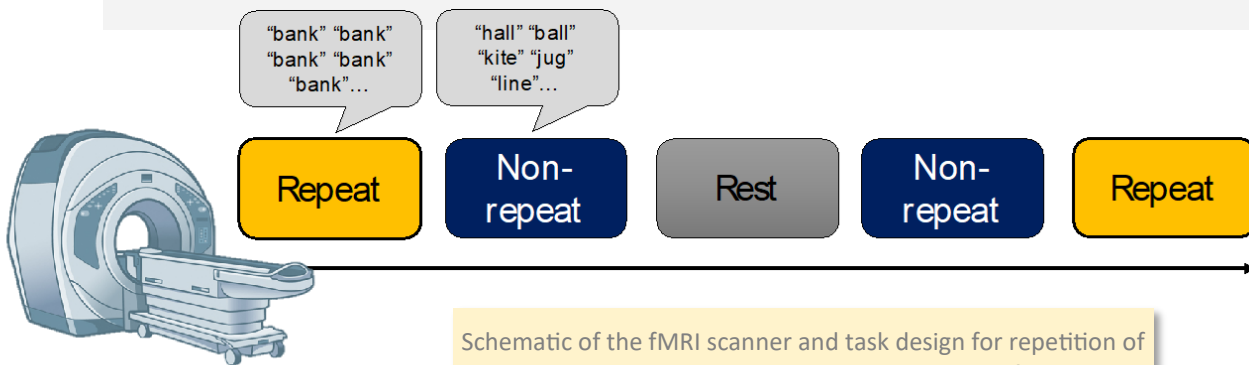
Prediction relies on the formation of expectations as a result of repeated experience. Recent evidence suggests that individuals with Autism Spectrum Disorder (ASD) may have difficulties predicting events and using predictions to optimize behavior. The development of expectations reduces the need to process repeated stimuli and results in decreased brain activation. Neural adaptation - reduced activation in the brain as a product of repetition - could be a mechanism that supports prediction by differentiating familiar from novel events.

My Simons Fellowship research investigates mechanisms of neural adaptation across social and non-social domains in individuals with autism. In the current study, we measure neural adaptation with functional magnetic resonance imaging (fMRI). We recruit adults with and without a diagnosis of autism to participate in an fMRI scan as well as a variety of cognitive assessments. As expected, our data shows that neural adaptation occurs primarily in stimulus-specific processing regions of cortex (e.g. superior temporal gyrus for speech). Importantly, our preliminary results suggest that there are strong correlations between autistic traits and neural adaptation measures.



Neural adaptation to speech is specific to regions of the brain that process speech (such as the superior temporal gyrus). These regions show reduced activation, or adaptation, for repeating speech.

Neural adaptation impairments are thought to contribute to multiple psychiatric and neurodevelopmental disorders, including schizophrenia and dyslexia. Knowledge gained from this research may therefore provide us with a better understanding of the neural underpinnings of neural adaptation in ASD as well as other neurodevelopmental disorders.



Schematic of the fMRI scanner and task design for repetition of spoken words. Repetition results in the build-up of strong expectations, and a decreased need to process repeated stimuli. Typically, this process is associated with decreased blood oxygen level dependent (BOLD) signal for the repeated stimulus in brain regions associated with processing the stimuli type.

UPCOMING EVENTS: SPRING 2019

COLLOQUIUM SERIES

FEBRUARY

13 - David Ginty, Ph.D.

Harvard Medical School; Howard Hughes Medical Institute

27 - David Leopold, Ph.D.

National Institute of Mental Health

MARCH

13 - Patricia Kuhl, Ph.D.

NSF Science of Learning Center, University of Washington

APRIL

3 - Craig Powell, M.D., Ph.D.

University of Alabama at Birmingham School of Medicine

17 - Nouchine Hadjikhani, M.D., Ph.D.

Harvard Medical School

MAY

15 - Guo-Li Ming, M.D., Ph.D.

Johns Hopkins University School of Medicine

29 - Baljit S. Khakh, Ph.D.

University of California, Los Angeles

LUNCH SERIES

- February 8, 2019 – **Nan Li, Ph.D.**
Postdoctoral Fellow, Alan Jasanoff Laboratory, MIT
- February 22, 2019 – **Danielle Tomasello, Ph.D.**
Simons Postdoctoral Fellow, Hazel Sive Laboratory, Whitehead Institute for Biomedical Research
- March 22, 2019 – **Nancy Padilla, Ph.D.**
Simons Postdoctoral Fellow, Kay Tye Laboratory, MIT
- April 12, 2019 – **Michael Halassa, Ph.D.**
Assistant Professor, Department of Brain & Cognitive Sciences, MIT
- May 10, 2019 – **Anila D’Mello, Ph.D.**
Simons Postdoctoral Fellow, John Gabrieli Laboratory, MIT

General Info:

Time: 12PM - 1PM

Location: SCSB Conference room, Building 46, Room 6011
43 Vassar Street, Cambridge, MA 02139

General Info:

Time: 4PM - 5PM, reception to follow

Location: Singleton Auditorium,
Building 46, Room 3002
43 Vassar Street, Cambridge, MA 02139

All events are open to the public, registration is not required



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